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Variation in Endoscopic Activity Assessment and Endoscopy Score Validation in Adults with Eosinophilic Esophagitis

Running head: *Endoscopy score for adults with EoE*

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Abbreviations used in this paper: Coeff, coefficient; CI, confidence interval; EEsAI, eosinophilic esophagitis activity index; EoE, eosinophilic esophagitis; EGD, esophagogastroduodenoscopy; EndoGA, endoscopist global assessment; EREFS, edema, rings, exudates, furrows and strictures; IQR, interquartile range; PRO, patient-reported outcome; ref, reference.

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ABSTRACT

Background & Aims: Eosinophilic esophagitis (EoE) is assessed endoscopically (endoscopic activity), based on grades of edema, rings, exudates, furrows, and strictures (EREFS). We examined variations in endoscopic assessments of severity, developed and validated 3 EREFS-based scoring systems, and assessed responsiveness of these systems using data from a randomized placebo-controlled trial of patients with EoE.

Methods: For the development set, 5 gastroenterologists reviewed EREFS findings from 266 adults with EoE and provided endoscopist global assessment scores (EndoGA, scale of 0 to 10); variation (∆EndoGA) was assessed using linear regression. We evaluated simple scores (features given arbitrary values from 0 to 3) and developed 2 scoring systems (adjusted score range, 0–100). We then fitted our linear regression model with mean EndoGA to data from 146 adults recruited in centers in Switzerland and the United States between April 2011 and December 2012. For the validation set, we collected data from 120 separate adults (recruited in centers in Switzerland and the United States between May 2013 and July 2014), assessing regression coefficient-based scores using Bland-Altman method. We assessed the responsiveness of our scoring systems using data from a randomized trial of patients with EoE given fluticasone (n=16) or placebo (n=8).

Results: The distribution of EndoGA values differed among endoscopists (mean ∆EndoGA, 2.6±1.8; range 0–6.6). We developed 2 regression-based scoring systems to assess overall and proximal and distal esophageal findings; variation in endoscopic features accounted for more than 90% of the mean EndoGA variation. In the validation group, differences between mean EndoGA and regression-based scores were small (ranging from –4.70 to 2.03), indicating good agreement. In analyses of data from the randomized trial, the baseline to end of study change in patients given fluticasone was a reduction of 24.3 in simple score (reduction of 4.6 in patients given placebo, *P*=.052); a reduction of 23.5 in regression-based overall score (reduction of 6.56 in patients given placebo, *P*=.12), and a reduction of 23.8 (reduction of 8.44 in patients given placebo, *P*=.11).

Conclusion: Assessments of endoscopic activity in patients with EoE vary among endoscopists. In an analysis of data from a randomized controlled trial, we found that newly developed scoring systems are no better than simple scoring system in detecting changes in endoscopic activity. These results support the use of a simple scoring system in evaluation of endoscopic activity in patients with EoE. clinicaltrials.gov no: NCT00939263 and NCT 01386112

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INTRODUCTION

Eosinophilic esophagitis (EoE) is defined as "a chronic, immune/antigen-mediated, esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation".[1,2,3]

As dysphagia is the most frequent complaint of adult EoE patients, esophagogastroduodenoscopy (EGD) represents an important diagnostic procedure.[1,2,3] Although endoscopic abnormalities are not pathognomonic of EoE, these are frequently assessed to aid in clinical decision making and interpretation of results of clinical trials and observational studies. In 2013, Hirano *et al.* described a classification and grading system of the following EoE-associated endoscopic alterations: edema, rings, exudates, furrows, and stricture(s) (EREFS).[4] While no score to assess the overall endoscopic activity was developed, attempts have been made to use the EREFS system as a basis for a simple score, which is calculated by summing together the arbitrary values from zero to three based on presence and severity of various EoE-associated features.[5,6] Dellon *et al.* reported that giving more weight to inflammatory features, such as exudates and edema, renders the EREFS-based score more responsive to anti-inflammatory treatment.[7] These studies revealed differences in the way gastroenterologists synthesize information about the severity of individual features when assessing overall endoscopic severity, and emphasize the importance of methodologic considerations in developing an endoscopic score.

Therefore, we used data from the adult EoE activity index (EEsAI) study population to explore the variation in gastroenterologists' assessment of endoscopic severity, used this information to develop and validate three EREFS-based scores, and assessed responsiveness of these scores using the data from randomized placebo-controlled clinical trial of fluticasone.[8]

PATIENTS AND METHODS

Study population

EEsAI study (clinicaltrials.gov ID:NCT00939263) was approved by local institutional review boards. The patient inclusion and exclusion criteria were previously published.[9]

Assessment of endoscopic findings

Distal and proximal esophageal sections were defined as those spanning 5 cm above the gastroesophageal junction and the top ½, respectively. Patients underwent EGD, during which endoscopic findings were assessed using EREFS system with modifications for stricture definitions (**Supplementary Table 1**).[4] The endoscopists performing EGD also provided the overall severity grading (absent, mild, moderate, severe).

Five endoscopists (AS, AMS, ESD, IH, YR, who performed ≥200 EGDs in EoE patients), were provided a datasheet containing the grading of inflammatory (white exudates, furrows, edema) and fibrotic (rings, strictures, crêpe-paper) features. The experts provided an Endoscopist Global Assessment (EndoGA) ranging 0-10 (0, inactive EoE; 10, most active EoE) as an overall impression of endoscopic severity.

Data handling and statistical analysis

Data were double-entered into EpiData (version 3.1) and imported into Stata (version 13.1) or R Project for analyses. Results are presented as percentages for categorical variables or median (interquartile range [IQR]) for continuous variables. The most severe category for a given feature found in either esophageal section represented 'overall' severity. If data on feature's severity in one esophageal section were missing, then that feature's severity in another section represented 'overall' severity.

Relationship between severity grading and EndoGA

We analyzed the relationship between EndoGA (outcome) and overall severity grading (fixed effect) using linear mixed-effects regression. We examined box plots of mean EndoGA for EGD performed in one's own center ($EndoGA^{own}$), in another center ($EndoGA^{others}$), and mean difference between $EndoGA^{own}$ and $EndoGA^{others}$ versus overall severity grading. We could not verify if physician 3 performed his/her patients' EGDs and dropped observations from that center for this analysis.

Variation in expert assessment of endoscopic severity

We examined the variation in the way endoscopists assessed overall endoscopic severity using several approaches. 1) The probability distributions of all EndoGA values provided by each expert were visualized using violin plots and boxplots. 2) To examine the per-patient variation, we calculated the difference between highest and lowest EndoGA values (∆EndoGA) from among five values assigned to findings of single EGD. A large ∆EndoGA value reflects disagreement in assessing that patient's endoscopic severity. To examine which features contributed most to per-patient variation, ∆EndoGA was regressed on each feature, and the coefficient of determination (R^2) was calculated. Features with a higher R^2 are more strongly associated with ∆EndoGA variance. A multivariable regression model with ∆EndoGA as outcome and all the features as predictors was used to examine each feature's contribution to variation in ∆EndoGA adjusted for all other features. 3) To assess the per-feature variation, we fitted a multivariable regression model to each expert's EndoGA values as outcome and the features as independent variables.

Development and validation of scores

We developed three EREFS-based scores (**Table 1**). For each patient, the mean of five EndoGA values was used as outcome.

Using the evaluation group data, the simple EREFS score ranging 0-8 was calculated (**Supplementary Table 1**). The scores were used as predictors for mean EndoGA in a linear regression, and the goodness of fit was assessed using R^2.

Using the evaluation group data, we developed two scores, the weighted EREFS score and the weighted EREFS-proximal/distal score, by fitting the predictors to the mean EndoGA scores using linear regression models. We assessed goodness of fit using R^2. The models' coefficients were used as values for the scores, which were transformed to range 0-100 (coefficients×100/∑all coefficients, rounded to 0.5). For weighted EREFS-proximal/distal score, most EREFS features were graded as described by Hirano *et al*.[4] The presence of crêpe-paper and the stricture severity were also examined. We also created the binary variables to indicate that most severe form of a feature is present in both esophageal

sections. We removed non-significant predictors from the model by backward elimination process. We also developed weighted scores using EndoGA^{own} as outcome.

To validate weighted scores (based on EndoGA or EndoGA^{own}), we used validation group data. The agreement between the EndoGA/EndoGA^{own} and the calculated score values was examined using the following plots: 1) Bland-Altman: (10×EndoGA-Score) versus (10×EndoGA+Score)/2 (the closer the horizontal line is to zero, the better is agreement between the measures); and 2) calibration: EndoGA/EndoGA^{own} versus score values (goodness of fit evaluated using R^2; for a perfect score the line fitted between EndoGA/EndoGA^{own} and score values has a slope of one). For each score, we also fit a linear regression model with score value as predictor and EndoGA^{own} as outcome. R^2 was calculated and meta-analyzed using a random effects meta-analysis model (R's "metafor" package). We estimated the R^2 variance using the CI.Rsq function (R's "psychometric" package) and calculated the standard error/confidence intervals of R^2 using a large sample approximation.[9]

Fluticasone clinical trial and scores' responsiveness

A randomized, double-blind, placebo-controlled trial (Phase 1b/2a) of fluticasone (APT-1011) examined the tolerability and safety of two APT-1011 dosing regimens compared to placebo in adolescent/adult EoE patients (clinicaltrials.gov ID: NCT01386112).[8] Subjects were randomized 1:1:1 to receive either APT-1011 1.5 mg BID (n=8), APT-1011 3.0 mg QD (n=8), or placebo (n=8). During EGDs at baseline and end of treatment (EOT) (week 8), EREFS were assessed. At EOT, the median esophageal eosinophil counts/mm^2 were significantly decreased from baseline in biopsies of patients given APT-1011 but not placebo (379 [IQR 289–563] to 0 [IQR 0–60] in APT-1011 1.5 mg BID, 378 [IQR 224–458] to 23 [IQR 0–109] in APT-1011 3.0 mg QD; and 459 [IQR 286–609] to 323 [IQR 200–523] in placebo). We examined scores' change (responsiveness) from baseline to EOT in drug-treated groups pulled together relative to placebo using ANCOVA models with time, treatment group, and an interaction term as fixed effects.

All authors had access to the study data and reviewed and approved the final manuscript.

RESULTS

The characteristics of 266 prospectively included adult EoE patients are shown in **Table 2**. The endoscopic characteristics of patients are shown in **Supplementary Table 2**.

The relationship between EndoGA and overall severity grading

We explored the relationship between overall severity grading and EndoGA (**Supplementary Figure 1**). We observed a two-point increase in predicted EndoGA for one level increase in a severity grading. This increase was independent of whether a physician performed EGD or ranked the EREFS findings provided by another physician. This is further confirmed by our finding that the mean difference between $EndoGA^{own}$ and $EndoGA^{others}$ values is centered around zero irrespective of the severity grading.

Variation in endoscopic activity assessment

When examining per-expert variation in EndoGA value distribution in the evaluation group (**Figure 1A**), we found that experts three, four, and five have a higher number of EndoGA values at the lower spectrum of severity. The mean EndoGA values (±SD and range) provided by endoscopists were: 4.35±2.91 (0-10); 3.55±2.18 (0-9); 2.27±1.96 (0-8.54); 3.51±2.46 (0-10); 3.44±2.50 (0-10).

The median ΔEndoGA for each patient's EGD was 2.29 (IQR 1.02-3.61, range 0-6.56). To evaluate which endoscopic features contributed most to ΔEndoGA variation, we examined the univariable linear regression R^2 values, which were as follows: exudates, R^2=0.411; rings, R^2=0.128; edema, R^2=0.347; furrows, R^2=0.299; strictures, R^2=0.002; stricture diameter, R^2=0.026, and crêpe-paper, R^2=0.043. Thus, exudates, edema, and furrows explained a relevant part of ΔEndoGA variation. Using multivariable analyses, we found that except for crêpe-paper (p-value=0.634), all the other features explained a part of ΔEndoGA variation (exudates, p-value<0.001; rings, p-value=0.003; edema, p-value<0.001; furrows, p-value=0.048; stricture diameter, p-value=0.03).

Lastly, we analyzed the variation in the way experts synthesize information about the presence/severity of endoscopic features by regressing each expert's EndoGA on the features (**Supplementary Table 3**, **Figure 1B**). The experts 'attributed' similar weights to the presence of furrows, edema, and crêpe-paper. For features with more than two severity

levels, we observed that the more severe the feature, the greater is the variation in the expert-attributed weights.

Development and validation of endoscopic scores

Simple EREFS scores

The median simple EREFS score in evaluation group was 3 (IQR 2–5, range 0-8). Using linear regression modelling in evaluation group, we found that a simple EREFS score explained 90.0% variation in the mean EndoGA (R^2=0.900, coefficient=1.100, 95% CI =1.040–1.161, intercept=-0.44). The crêpe-paper addition did not improve this performance. The correlation between the mean EndoGA values and simple EREFS-based scores are shown in **Supplementary Figure 2**.

Weighted EREFS scores

We then developed an EREFS-based score estimating the weights that expert endoscopists attributed to various features (**Table 3**). The variation in the severity of major endoscopic features explained 91.6% variation in EndoGA. The model's coefficients were used as the values for the score (transformed to range 0-100). In the validation group, the weighted EREFS score explained 89.2% of the mean EndoGA variation (**Figure 2A**). In Bland-Altman plot, the mean difference of -4.70 between weighted EREFS score and the mean EndoGA was observed (95% CI:10.46, -19.86) (**Figure 2B**). The crêpe-paper addition had a small impact on weighted score (**Figure 2C/D**). If validation was carried out using $EndoGA^{own}$ as an outcome, the weighted EREFS score explained 80.0% (meta-analyzed R^2, **Supplementary Figure 3B**) and 77.1% (**Supplementary Figure 4A**) of the mean $EndoGA^{own}$ variation. In Bland-Altman analyses, the mean difference of -3.54 between weighted EREFS score and the mean $EndoGA^{own}$ was observed (95% CI: 20.74, -27.81) (**Supplementary Figure 4B**).

Weighted EREFS-proximal/distal score

We developed a weighted EREFS score that considered stricture severity and presence of crêpe-paper. The variation in the severity of different features explained 95.9% variation in EndoGA (R^2=0.959). Using backwards elimination, crêpe-paper and furrowing were removed, with only a minor change in R^2 (**Table 4**). The final model's coefficients were used

as the values for the score (transformed to range 0-100). In the validation group, the weighted EREFS-proximal/distal score estimated 94.8% of the mean EndoGA (**Figure 2E**). In Bland-Altman plot, mean difference of 2.03 between weighted EREFS-proximal/distal score and the mean EndoGA was observed (95% CI: 12.12, -8.05) (**Figure 2F**). If validation was carried out using EndoGA^{own} as an outcome, the weighted EREFS-proximal/distal score explained 85% of the mean EndoGA^{own} variation (meta-analyzed R^2 in **Supplementary Figure 3C**; **Supplementary Figure 4C**). In Bland-Altman analyses, the mean difference of 3.46 between weighted EREFS-proximal/distal score and the mean EndoGA^{own} was observed (95% CI: 24.12, -17.21) (**Supplementary Figure 4D**).

The data on development and validation of the weighted scores based on EndoGA^{own} as outcome are shown in **Supplementary Tables 5** and **6**, and **Supplementary Figure 5**.

Scores' Responsiveness

The rate of baseline to EOT change in fluticasone-treated patients (n=16) (relative to placebo [n=8], p-value) was -24.3 (-4.6, p-value=0.052), -23.5 (-6.56, p-value=0.12), and -23.8 (-8.44, p-value=0.11) for simple EREFS score, weighted EREFS score, and weighted EREFS-proximal/distal scores, respectively (**Supplementary Table 4**). We separately examined the effect treatment had on inflammatory and fibrotic features. The slope analysis detected significant treatment benefit over placebo on inflammatory features, when using simple but not weighted scores.

DISCUSSION

As consensus on grading endoscopic severity in currently published studies is lacking, we evaluated three EREFS-based scores for endoscopic activity assessment in adults with EoE. We found that: 1) overall impression of EoE endoscopic severity differs among endoscopists; 2) the simple score explained the overall variation of endoscopic severity to a similar extent compared to the weighted scores; and 3) when evaluating scores' responsiveness in a clinical trial, the weighted scores were statistically no better than the simple EREFS score in differentiating fluticasone- from placebo-treated patients. Hence, the simple score should be used in short-term clinical trials of anti-inflammatory therapies. Whether weighted EREFS-proximal/distal score should be used in long-term trials and studies remains to be elucidated. As for clinical practice, we advocate for the use of simple score, as the convenience of using it outweighs the modest gains in "precision" provided by newly-developed scores.

The study's findings have important implications for endoscopic activity assessment. Exudates contributed most to the per-endoscopist variation in activity assessment. Compared to simple score, new scores put more weight on exudates and less on the furrows, which is consistent with symptom severity in the same population.[10] We observed no benefit in scoring crêpe-paper, whereas inclusion of stricture diameter is of importance, as persons with intermediate-/high-grade strictures experience severe symptoms and diminished EoE-specific quality of life.[10,11] Values attributed to furrows and edema should not be doubled, as previously suggested.[7] Inclusion of variables that account for the endoscopic severity in both esophageal sections resulted in statistically best score. Whether assessment of endoscopic findings in both esophageal sections is of benefit remains to be determined. The weighted scores derived based on endoscopic activity assessment of the physician performing EGD are statistically more heterogeneous and likely to provide less consistent results, when compared to the scores derived based on expert group judgement.

The optimal approach to assessing furrows severity using EREFS system is a subject of much research. Hirano *et al.* reported that interobserver agreement for distinguishing between mild and severe furrows was moderate; hence, these categories were collapsed for

the final EREFS system.[4] Nevertheless, both types of furrows severity grading have been previously reported. Dellon *et al.* graded furrows severity as absent, mild, and severe in both an observational study and budesonide clinical trial.[6,7] In contrast, van Rhijn *et al.* graded furrows as absent/present.[5] These studies also evaluated EREFS-based scores' responsiveness to treatment.[5-7] Given that many EoE therapies are anti-inflammatory, researchers increased the weight of inflammatory features. For example, Dellon *et al.* demonstrated that doubling the points attributed to exudates and edema improved the score responsiveness.[7]

Therefore, we developed weighted EREFS scores that incorporate expert considerations in a population larger than used previously (266 compared to 93, 67, and 69 patients, respectively).[5-7] Compared to the simple score, experts weighted severe exudates more than in previous studies but furrows and edema similarly. Our data are similar to those on symptom severity, as patients with severe exudates experience worse EoE-specific quality of life and severe symptoms.[10,11] In contrast, quality of life and symptoms of patients, in whom furrows and edema are present, don't differ from those of patients lacking these features.[9,10] We found that weighted EREFS-proximal/distal score correlates best with EndoGA and has the smallest mean difference and limits of agreement, but it was no better at detecting fluticasone treatment benefit than a simple score.

Endoscopists provided EndoGA by examining a datasheet containing the summary of endoscopic findings to prevent the ambiguities in EREFS ranking, which would preclude us from developing a score (like equation with two unknowns). However, experts' EndoGA was strongly associated with the severity grading obtained directly after the EGD, and the increase in EndoGA associated with increase in the severity grading was independent of whether physician performed EGD or ranked the EREFS findings provided by another physician.

Our study has strengths and limitations. The data provided to the experts included all EREFS features, and these were used as predictors for score development; therefore, as expected, large part of the variance is explained by these variables. In our study, the stricture diameter was estimated relative to endoscope diameter. Future studies should

assess the stricture diameter using balloons, bougies, or the functional luminal imaging probe. The scores' responsiveness was evaluated using the data from the trial, into which patients with relatively mild disease activity were included. We wonder, if weighed scores were to perform differently, if patients with more severe disease were included. Nevertheless, the study's limitations are countered by strengths including a large sample size, inclusion of independent group for score validation, attempt to seek consensus among experts, and scores' responsiveness assessment using clinical trial data.

In summary, we examined various scores for endoscopic activity assessment in adult EoE patients. The new scores were no better in detecting the fluticasone treatment benefit over placebo compared to a simple EREFS score. These results suggest that the simple EREFS score should be used in short-term, clinical trials of anti-inflammatory therapies.

TABLES

Table 1: Summary of the developed scores.

	Simple EREFS score	**Weighted EREFS score**	**Weighted EREFS-proximal/distal score**
Takes into account expert considerations	No	Yes	Yes
Statistical methods for score derivation	Not applicable	Linear regression with mean of five EndoGA values as outcome	Linear regression with mean of five EndoGA values as outcome
Worst endoscopic presentation represents overall endoscopic severity for that feature	Yes	Yes	No, severity of endoscopic features is assessed in both proximal and distal esophagus by introducing extra variables denoting presence of endoscopic features in both parts of the esophagus
Validation	Not applicable	Validated in second independent group of patients	Validated in second independent group of patients
Responsiveness	Yes, evaluated using data from short-term randomized placebo-controlled clinical study of fluticasone	Yes, evaluated using data from short-term randomized placebo-controlled clinical study of fluticasone	Yes, evaluated using data from short-term randomized placebo-controlled clinical study of fluticasone
Components of the score	Rings none mild moderate severe Exudates none mild	Rings none mild moderate severe Exudates none mild	Rings none mild in prox. and/or dist. moderate in prox. and/or dist. severe in prox. and/or dist. Exudates none mild in prox. and/or dist.

	severe	severe	severe in prox. and/or dist.
	Furrows	Furrows	Edema
	absent	absent	absent
	present	present	present in prox. and/or dist..
	Edema	Edema	Crêpe-paper
	absent	absent	absent
	present	present	present in prox. and/or dist.
	Strictures	Strictures	Strictures
	absent	absent	absent
	present	present	low-grade in prox. and/or dist.
	(Crêpe paper	(Crêpe paper	intermediate /high in prox. and/or dist.
	absent	absent	Severe rings
	present)	present)	absent in prox. and dist.
			present in prox. and dist.
			Severe exudates
			absent in prox. and dist.
			present in prox. and dist.
			Furrows
			absent in prox. and dist.
			present in prox. and dist.
			Edema
			absent in prox. and dist.
			present in prox. and dist.

Abbreviations: dist., distal part of esophagus; EREFS, edema, rings, exudates, furrows, and strictures; EndoGA, endoscopist global assessment; prox., proximal part of esophagus.

Table 2: Patient characteristics.

Characteristic	Evaluation group Frequency	%	Validation group Frequency	%
Number of patients	146	(100.0)	120	(100.0)
Males	104	(71.2)	73	(60.8)
Age at inclusion (median, interquartile range, range)	37.7	(29 - 46; 18 - 71)	40.5	(31 - 49; 19 - 80)
Ethnicity				
White	142	(97.3)	114	(95.0)
Non-white	4	(2.7)	6	(5.0)
Education				
Compulsory schooling	2	(1.4)	1	(0.8)
Vocational training	36	(24.7)	33	(27.5)
Upper secondary education	63	(43.2)	54	(45.0)
University education	45	(30.8)	32	(26.7)
Eosinophilic esophagitis symptoms onset				
1 to 11 months ago	8	(5.5)	2	(1.7)
1 to 5 years ago	61	(41.8)	38	(31.7)
more than 5 years ago	77	(52.7)	80	(66.6)
Clinical activity (EEsAI PRO score, range 0 - 100)	27	(12-46; 0-94)	27	(6-42; 0-94)
Peak esophageal eosinophil count per mm^2 (median, interquartile range, range)	95	(26 – 226; 0 - 744)	87	(11 – 305; 0 – 1558)
Allergic diseases / Allergies				
Asthma	53	(36.3)	42	(35.0)
Rhinoconjunctivitis	87	(59.6)	72	(60.0)
Eczema	18	(12.3)	34	(28.3)
Food allergy	43	(29.5)	60	(50.0)
Gastro-esophageal reflux disease	45	(30.8)	18	(15.0)
Diagnosis established:				
Clinically	26	(57.8)	3	(16.7)
Endoscopically	11	(24.4)	6	(33.3)
Based on pH-metric studies	1	(2.2)	2	(11.1)
Clinically and endoscopically	8	(17.8)	5	(27.8)
Concomitant medications				
Proton-pump inhibitors	80	(54.8)	39	(32.5)
Histamine antagonists (H_2-receptor)	5	(3.4)	1	(0.8)
Histamine antagonists (H_1-receptor)	24	(16.4)	18	(15.0)
Inhaled corticosteroids for asthma	4	(2.7)	4	(3.3)
β2-adrenergic agonists for asthma	21	(14.4)	2	(1.7)
Leukotriene receptor antagonists for asthma	4	(2.7)	1	(0.8)
EoE-specific treatments in the last 12 months	86	(58.9)	103	(85.8)
Hypo-allergenic diets	17	(11.6)	19	(15.8)
Swallowed topical corticosteroids	62	(42.5)	78	(65.0)
Esophageal dilation	27	(18.5)	26	(21.7)

Abbreviations: EEsAI, eosinophilic esophagitis activity index; PRO, patient-reported outcomes.

Table 3: Multivariable linear regression model for derivation of weighted EREFS scores (with and without crêpe-paper). Final scores.

	Coefficient[a]	95% CI	P-value	Score (total set to 100)	Coefficient[a]	95% CI	P-value	Score (total set to 100)
Rings								
none	0.000	Ref.		0	0.000	Ref.		0
mild	1.239	0.941 – 1.538	<0.001	13	1.223	0.937 – 1.510	<0.001	12.5
moderate	2.169	1.807 – 2.531	<0.001	23	2.132	1.784 – 2.480	<0.001	22
severe	3.332	2.773 – 3.890	<0.001	35.5	3.216	2.677 – 3.756	<0.001	33.5
Exudates								
none	0.000	Ref.		0	0.000	Ref.		0
mild	1.341	1.058 – 1.624	<0.001	14	1.373	1.101 – 1.645	<0.001	14
severe	3.155	2.685 – 3.625	<0.001	33.5	3.082	2.629 – 3.534	<0.001	32
Furrows								
absent	0.000	Ref.		0	0.000	Ref.		0
present	0.586	0.277 – 0.896	<0.001	6	0.608	0.311 – 0.906	<0.001	6.5
Edema								
absent	0.000	Ref.		0	0.000	Ref.		0
present	1.232	0.939 – 1.524	<0.001	13	1.128	0.841 – 1.414	<0.001	11.5
Strictures								
absent	0.000	Ref.		0	0.000	Ref.		0
present	1.117	0.822 – 1.411	<0.001	12	0.965	0.671 – 1.260	<0.001	10
Crêpe-paper	NA	NA	NA	NA				
absent					0.000	Ref.		0
present					0.652	0.292 – 1.013	<0.001	6.5
Constant[b]	0.044	-0.201 – 0.289	0.722		0.078	-0.158 – 0.314	0.514	
R^2[c]	0.916				0.923			
Sum of the coefficients/ Score	9.422			100	9.651			100

Abbreviations: CI, confidence interval; EndoGA, endoscopist global assessment; Ref. reference.

[a] The coefficient represents the EndoGA value change for each endoscopic feature. For example, mean EndoGA increased by 1.239, if mild rings were found. In these analyses, the adjusted regression coefficient for rings represents the amount of mean EndoGA variation that is owing to the rings alone, after the presence of all other features was considered. If mild rings and edema were detected, then mean EndoGA increased by 2.471 (1.239 for mild rings and 1.232 for edema).

[b] The constant represents the predicted EndoGA value, when all values of independent variables are set to reference category.

[c] R^2 is a measure of the extent to which the regression model describes the data. The closer R^2 is to one, the more precise the regression model is.

Table 4: Multivariable linear regression model for derivation of the weighted EREFS-proximal/distal score. Model 1 includes all predictors, whilst models 2 and 3 are fitted to the data after exclusion of the least significant features. Final score.

	Model 1			Model 2			Model 3			Score
	Coeff[a]	95% CI	P-value	Coeff[a]	95% CI	P-value	Coeff[a]	95% CI	P-value	(total set to 100)
Rings										
none	0.000	Ref.	<0.001	0.000	Ref.	<0.001	0.000	Ref.	<0.001	0
mild in prox. and/or dist.	1.018	0.796 – 1.241		1.018	0.796 – 1.240		1.022	0.801 – 1.242		10
moderate in prox. and/or dist.	1.871	1.605 – 2.136		1.871	1.607 – 2.136		1.875	1.612 – 2.138		18
severe in prox. and/or dist.	1.703	1.043 – 2.362		1.678	1.034 – 2.322		1.677	1.034 – 2.319		18
Exudates										
none	0.000	Ref.	<0.001	0.000	Ref.	<0.001	0.000	Ref.	<0.001	0
mild in prox. and/or dist.	1.525	1.316 – 1.734		1.524	1.316 – 1.732		1.537	1.337 – 1.738		15
severe in prox. and/or dist.	2.021	1.402 – 2.639		2.042	1.436 – 2.648		2.055	1.453 – 2.657		19.5
Furrows							-	-	-	-
absent	0.000	Ref.	0.653	0.000	Ref.	0.633				
present in prox. and/or dist.	0.082	-0.278 – 0.441		0.087	-0.271 – 0.444					
Edema										
absent	0.000	Ref.	0.048	0.000	Ref.	0.050	0.000	Ref.	0.009	0
present in prox. and/or dist..	0.475	0.005 – 0.944		0.464	0.000 – 0.929		0.526	0.136 – 0.915		5
Crêpe-paper										
absent	0.000	Ref.	0.045	0.000	Ref.	<0.001	0.000	Ref.	<0.001	0
present in prox. and/or dist.	0.471	0.011 – 0.931		0.540	0.254 – 0.826		0.534	0.250 – 0.818		5
Strictures										
absent	0.000	Ref.	<0.001	0.000	Ref.	<0.001	0.000	Ref.	<0.001	0
low-grade in prox. and/or dist.	0.836	0.612 – 1.060		0.835	0.612 – 1.058		0.836	0.613 – 1.058		8
intermediate /high in prox. and/or dist.	1.875	1.426 – 2.324		1.872	1.425 – 2.319		1.866	1.421 – 2.311		18
Severe rings										
absent in prox. and dist.	0.000	Ref.	0.017	0.000	Ref.	0.013	0.000	Ref.	0.011	0
present in prox. and dist.	0.776	0.141 – 1.410		0.795	0.170 – 1.419		0.808	0.188 – 1.429		8

	Model 1			Model 2			Model 3			Score (total set to 100)
	Coeff[a]	**95% CI**	**P-value**	**Coeff**[a]	**95% CI**	**P-value**	**Coeff**[a]	**95% CI**	**P-value**	
Severe exudates										
absent in prox. and dist.	0.000	Ref.	<0.001	0.000	Ref.	<0.001	0.000	Ref.	<0.001	0
present in prox. and dist.	1.377	0.650 – 2.104		1.342	0.641 – 2.043		1.333	0.635 – 2.031		13
Furrows										
absent in prox. and dist.	0.000	Ref.	<0.001	0.000	Ref.	<0.001	0.000	Ref.	<0.001	0
present in prox. and dist.	0.893	0.539 – 1.248		0.891	0.538 – 1.244		0.958	0.735 – 1.181		9
Edema										
absent in prox. and dist.	0.000	Ref.	0.039	0.000	Ref.	0.031	0.000	Ref.	0.027	0
present in prox. and dist.	0.508	0.025 – 0.990		0.522	0.047 – 0.997		0.465	0.055 – 0.875		4.5
Crêpe-paper				-	-	-	-	-	-	-
absent in prox. and dist.	0.000	Ref.	0.707							
present in prox. and dist.	0.101	-0.429 – 0.630								
Constant	0.193	0.131 – 0.374	0.036	0.192	0.122 – 0.371	0.037	0.201	0.027 – 0.376	0.024	-
R^2	0.959			0.959			0.958			
Sum							10.419			100

Abbreviations: Coeff, coefficient; CI, confidence interval; dist., distal; EndoGA, endoscopist global assessment; prox., proximal; Ref. reference.

FIGURES

Figure 1: A. The distribution of global assessment values provided by endoscopists. The vertical lines indicate the interquartile range; the crossing horizontal line is at the median. Rhombi indicate the mean. **B.** Variation in the weights that five endoscopists attribute to different endoscopic features.

Figure 2: The calibration plots for (**A**) weighted EREFS, (**C**) weighted EREFS with crêpe-paper (EREFSC), and (**E**) weighted EREFS-proximal/distal (EREFS-PD) scores in the validation group. The solid line has a slope of one and represents an ideal relationship between a perfect score and EndoGA values. The dashed line is the regression line fit to the data. Bland–Altman plots for the agreement between (**B**) weighted EREFS, (**D**) weighted EREFSC, (**F**) weighted EREFS-PD scores and 10×EndoGA in the validation group. The grey box indicates the 95% confidence intervals limits of agreement.

Supplementary Figure 1: The relationship between EndoGA and overall severity grading: **A.** Relationship between fixed portion of estimated EndoGA and overall severity grading. The vertical lines indicate the 95% confidence interval. The box-and-whiskers plots of (**B**) mean difference between EndoGA for EGD performed in one's own center ($EndoGA^{own}$) and EndoGA for EGD performed in another center ($EndoGA^{others}$), (**C**) $EndoGA^{own}$, (**D**) $EndoGA^{others}$ versus overall severity grading.

Supplementary Figure 2: The correlation between the simple EREFS scores and EndoGA without the crêpe-paper (**A**) and with crêpe-paper (**B**) in the evaluation group.

Supplementary Figure 3: The meta-analyzed R^2 values for (**A**) simple EREFS score, (**B**) weighted EREFS score, and (**C**) weighted EREFS-proximal/distal score.

Supplementary Figure 4: The calibration plots of $EndoGA^{own}$ versus the weighted scores in the validation group: (**A**) weighted EREFS score, (**C**) weighted EREFS-proximal/distal (EREFS-PD) score. The solid line has a slope of one and represents an ideal relationship between a perfect score and EndoGA values. The dashed line is the regression line fit to the data. The Bland–Altman plots for the agreement between the weighted scores and 10×EndoGA in the validation group: (**B**) weighted EREFS score, (**D**) weighted EREFS-PD score. The grey box indicates the 95% confidence intervals limits of agreement.

Supplementary Figure 5: The calibration plots of EndoGA^{own} versus for the weighted scores developed based on EndoGA^{own} in the validation group: (**A**) weighted EREFS score, (**C**) weighted EREFS-proximal/distal (EREFS-PD) score. The solid line has a slope of one and represents an ideal relationship between a perfect score and EndoGA values. The dashed line is the regression line fit to the data. The Bland–Altman plots for the agreement between the weighted scores and 10×EndoGA in the validation group: (**B**) weighted EREFS score, (**D**) weighted EREFS-PD score. The grey box indicates the 95% confidence intervals limits of agreement.

SUPPLEMENTARY TABLES

Supplementary Table 1: The EREFS classification and grading system-based score. In addition to absence/presence of strictures, we evaluated whether low-grade, intermediate-grade, or high-grade stricture(s) were found.

Feature	Grading	Definition	Points
Major features			
Rings *(< 1 cm length)*	Grade 0	None	0
	Grade 1	Mild (subtle circumferential ridges)	1
	Grade 2	Moderate (distinct rings that do not impair passage of a standard diagnostic adult endoscope [outer diameter 8-10 mm])	2
	Grade 3	Severe (distinct rings that do not permit passage of a diagnostic endoscope)	3
Exudates	Grade 0	None	0
	Grade 1	Mild (lesions involving <10% of the esophageal surface area)	1
	Grade 2	Severe (lesions involving >10% of the esophageal surface area)	2
Furrows	Grade 0	Absent	0
	Grade 1	Present	1
Edema	Grade 0	Absent (distinct vascularity present)	0
	Grade 1	Loss of clarity or absence of vascular markings	1
Stricture *(≥ 1 cm length)*	Grade 0	Absent	0
	Grade 1	Present	1
	OR	**OR**	
	Grade 0	None	NA
	Grade 1	Low-grade (esophageal diameter 11-13 mm, passage of standard endoscope possible against mild resistance)	NA
	Grade 2	Intermediate-grade (esophageal diameter 7-10 mm, passage of a 6-mm outer diameter endoscope possible, but impossible with standard endoscope [8-10-mm outer diameter])	NA
	Grade 3	High-grade (passage of a 6-mm outer diameter endoscope is not possible)	NA
Total score			**8**
Minor feature			
Crêpe-paper	Grade 0	Absent	0
	Grade 1	Present	1
Total score including crêpe paper			**9**

Abbreviations: NA, not applicable.

Supplementary Table 2: Endoscopic findings in proximal and distal esophagus as well as in esophagus 'overall' in all patients, evaluation and validation groups.

Characteristic		Proximal		Distal		Overall	
		Frequency	%	Frequency	%	Frequency	%
Endoscopic findings (n=266)							
Rings:	Absent	104	39.1	81	30.5	74	27.8
	Mild	89	33.5	99	37.2	99	37.2
	Moderate	58	21.8	73	27.4	77	28.9
	Severe	12	4.5	12	4.5	16	6.0
	Missing	3	1.1	1	0.4	0	0.0
Strictures:	Absent	223	83.8	192	72.2	178	66.9
	Present	40	15.0	73	27.4	88	33.1
	Missing	3	1.1	1	0.4	0	0.0
Exudates:	Absent	205	77.1	183	68.8	177	66.5
	Mild	46	17.3	67	25.2	73	27.4
	Severe	14	5.3	14	5.3	16	6.0
	Missing	1	0.4	2	0.8	0	0.0
Furrows:	Absent	137	51.5	105	39.5	102	38.3
	Present	128	48.1	160	60.2	164	61.7
	Missing	1	0.4	1	0.4	0	0.0
Edema:	Absent	140	52.6	114	42.9	113	42.5
	Present	125	47.0	151	56.8	153	57.5
	Missing	1	0.4	1	0.4	0	0.0
Crêpe-paper:	Absent	239	89.8	239	89.8	234	88.0
	Present	26	9.8	26	9.8	32	12.0
	Missing	1	0.4	1	0.4	0	0.0
Endoscopic findings (evaluation group, n=146)							
Rings:	Absent	54	37.0	44	30.1	39	26.7
	Mild	46	31.5	54	37.0	53	36.3
	Moderate	36	24.7	40	27.4	44	30.1
	Severe	8	5.5	7	4.8	10	6.8
	Missing	2	1.4	1	0.7	0	0.0
Strictures:	Absent	117	80.1	104	71.2	96	65.8
	Present	27	18.5	41	28.1	50	34.2
	Missing	2	1.4	1	0.7	0	0.0
Exudates:	Absent	108	74.0	100	68.5	97	66.4
	Mild	28	19.2	36	24.7	39	26.7
	Severe	9	6.2	8	5.5	10	6.8
	Missing	1	0.7	2	1.4	0	0.0
Furrows:	Absent	62	42.5	50	34.2	49	33.6
	Present	83	56.8	95	65.1	97	66.4
	Missing	1	0.7	1	0.7	0	0.0
Edema:	Absent	67	45.9	61	41.8	61	41.8
	Present	78	53.4	84	57.5	85	58.2
	Missing	1	0.7	1	0.7	0	0.0
Crêpe-paper:	Absent	129	88.4	129	88.4	127	87.0
	Present	16	11.0	16	11.0	19	13.0

	Missing	1	0.7	1	0.7	0	0.0
Endoscopic findings (validation group, n=120)							
Fixed rings:	Absent	50	41.7	38	31.7	35	29.2
	Mild	43	35.8	44	36.7	46	38.3
	Moderate	22	18.3	33	27.5	33	27.5
	Severe	4	3.3	5	4.2	6	5.0
	Missing	1	0.8	0	0.0	0	0.0
Strictures:	Absent	97	80.8	82	68.3	80	66.7
	Present	18	15.0	32	26.7	34	28.3
	Missing	5	4.2	6	5.0	6	5.0
Exudates:	Absent	0	0.0	0	0.0	0	0.0
	Mild	106	88.3	86	71.7	82	68.3
	Severe	13	10.8	34	28.3	38	31.7
	Missing	1	0.8	0	0.0	0	0.0
Furrows:	Absent	75	62.5	55	45.8	53	44.2
	Present	45	37.5	65	54.2	67	55.8
	Missing	0	0.0	0	0.0	0	0.0
Edema:	Absent	73	60.8	53	44.2	52	43.3
	Present	47	39.2	67	55.8	68	56.7
	Missing	0	0.0	0	0.0	0	0.0
Crêpe-paper:	Absent	110	91.7	110	91.7	107	89.2
	Present	10	8.3	10	8.3	13	10.8
	Missing	0	0.0	0	0.0	0	0.0

Supplementary Table 3: Multivariable linear regression model with endoscopist global assessment as an outcome and endoscopic features (dependent variables) – one for each expert endoscopist.

	Expert 1			Expert 2			Expert 3			Expert 4			Expert 5		
	Coeff	**95% CI**	**P**	**Coeff**	**95% CI**	**P**	**Coeff**	**95% CI**	**P**	**Coeff**	**95% CI**	**P**	**Coeff**	**95% CI**	**P**
Rings															
none	0.000	Ref.		0.000	Ref.		0.000	Ref.		0.000	Ref.		0.000	Ref.	
mild	1.219	0.773 – 1.664	<0.001	1.917	1.575 – 2.259	<0.001	0.879	0.596 – 1.162	<0.001	1.083	0.693 – 1.474	<0.001	1.113	0.697 – 1.529	<0.001
moderate	3.049	2.516 – 3.583	<0.001	2.755	2.345 – 3.164	<0.001	1.683	1.344 – 2.023	<0.001	1.614	1.146 – 2.082	<0.001	1.576	1.077 – 2.075	<0.001
severe	3.672	2.600 – 4.743	<0.001	3.147	2.325 – 3.969	<0.001	2.694	2.013 – 3.375	<0.001	1.883	0.943 – 2.822	<0.001	1.722	0.721 – 2.723	<0.001
Strictures															
absent	0.000	Ref.		0.000	Ref.		0.000	Ref.		0.000	Ref.		0.000	Ref.	
low-grade	0.532	0.069 – 0.994	0.025	0.625	0.271 – 0.980	0.001	1.578	1.284 – 1.872	<0.001	0.749	0.347 – 1.151	<0.001	0.591	0.163 – 1.020	0.007
intermediate /high	1.302	0.395 – 2.208	0.005	0.962	0.267 – 1.658	0.007	3.064	2.487 – 3.640	<0.001	1.975	1.180 – 2.770	<0.001	0.875	0.028 – 1.721	0.043
Exudates															
none	0.000	Ref.		0.000	Ref.		0.000	Ref.		0.000	Ref.		0.000	Ref.	
mild	1.593	1.171 – 2.015	<0.001	0.479	0.155 – 0.803	0.004	0.295	0.027 – 0.563	0.031	2.097	1.729 – 2.466	<0.001	2.284	1.892 – 2.676	<0.001
severe	3.586	2.885 – 4.288	<0.001	2.470	1.932 – 3.008	<0.001	0.638	0.191 – 1.084	0.005	3.947	3.332 – 4.562	<0.001	4.410	3.754 – 5.065	<0.001
Furrows															
absent	0.000	Ref.		0.000	Ref.		0.000	Ref.		0.000	Ref.		0.000	Ref.	
present	0.878	0.413 – 1.344	<0.001	1.100	0.741 – 1.455	<0.001	0.511	0.215 – 0.807	0.001	0.556	0.148 – 0.964	0.008	0.515	0.080 – 0.949	0.021
Edema															
absent	0.000	Ref.		0.000	Ref.		0.000	Ref.		0.000	Ref.		0.000	Ref.	
present	1.607	1.164 – 2.050	<0.001	1.021	0.681 – 1.361	<0.001	0.319	0.037 – 0.601	0.027	1.165	0.776 – 1.553	<0.001	1.287	0.873 – 1.701	<0.001
Crêpe-paper															
absent	0.000	Ref.		0.000	Ref.		0.000	Ref.		0.000	Ref.		0.000	Ref.	
present	0.789	0.212 – 1.366	0.008	-0.502	-0.493 – 0.392	0.823	0.352	-0.014 – 0.720	0.059	0.701	0.196 – 1.205	0.007	0.930	0.393 – 1.468	0.001
Constant	0.209	-0.157 – 0.574	0.261	-0.037	-0.317 – 0.244	0.796	-0.111	-0.343 – 0.122	0.348	0.147	-0.174 – 0.467	0.367	0.086	-0.256 – 0.427	0.621
R^2	0.890			0.885			0.902			0.882			0.870		

Abbreviations: CI, confidence interval; Ref. reference.
The constant represents the predicted EndoGA value, when all values of independent variables are set to reference category.
R^2 is a measure of the extent to which the regression model describes the observed data. The closer R^2 is to one, the more precise the regression model is.

Supplementary Table 4: Responsiveness of the developed scores.

	Baseline to end of treatment slope of change in drug-treated group (converted from 0 to 100 for simple score)	**Baseline to end of treatment slope of change in placebo group-treated group (converted from 0 to 100 for simple score)**	**p-value**
Simple EREFS total score	-1.94 (-24.3)	-0.37 (-4.6)	0.052
Simple EREFS inflammatory*	-1.62 (-20.3)	-0.37 (-4.6)	0.04
Simple EREFS fibrotic*	-0.31 (3.9)	0.00 (0.0)	0.62
Weighted EREFS total score	-23.5	-6.6	0.12
Weighted EREFS inflammatory*	-19.9	-6.9	0.13
Weighted EREFS fibrotic*	-3.6	0.4	0.59
Weighted EREFS-proximal/distal score total score	-23.8	-8.4	0.11
EREFS-proximal/distal score inflammatory*	-20.8	-10.6	0.17
Weighted EREFS-proximal/distal score fibrotic*	-3.1	2.1	0.39

***** In addition to the overall EREFS-based scores, we also separately examined the treatment effect on inflammatory endoscopic features (exudates, furrows, and edema) and fibrotic endoscopic features (rings, strictures, [and crêpe-paper for EREFS-proximal/distal score]).

Supplementary Table 5: Weighted EREFS scores based on average of five values of EndoGA and single EndoGA^{own} values.

	Weighted EREFS score based on average of 5 values of EndoGA (total set to 100)	**New weighted EREFS score based on EndoGA^{own} (total set to 100)**
Rings		
none	0	0
mild	13	12
moderate	23	19
severe	35.5	33.5
Exudates		
none	0	0
mild	14	18
severe	33.5	38
Furrows		
absent	0	0
present	6	6
Edema		
absent	0	0
present	13	11
Strictures		
absent	0	0
present	12	11.5
Sum of the score	100	100

Supplementary Table 6: Weighted EREFS-proximal/distal scores based on average EndoGA and single EndoGA^{own} values.

	Based on average value of 5 EndoGA values Score (total set to 100)	**New based on EndoGA^{own} Score (total set to 100)**
Rings		
none	0	0
mild in prox. and/or dist.	10	8
moderate in prox. and/or dist.	18	13.5
severe in prox. and/or dist.	18	24
Exudates		
none	0	0
mild in prox. and/or dist.	15	18.5
severe in prox. and/or dist.	19.5	24.5
Furrows	-	-
absent		
present in prox. and/or dist.		
Edema		-
absent	0	
present in prox. and/or dist.	5	
Crêpe-paper		
absent	0	0
present in prox. and/or dist.	5	6.5
Strictures		
absent	0	0
low-grade in prox. and/or dist.	8	7.5
intermediate /high in prox. and/or dist.	18	14.5
Severe rings		
absent in prox. and dist.	0	0
present in prox. and dist.	8	-12
Severe exudates		
absent in prox. and dist.	0	0
present in prox. and dist.	13	13.5
Furrows		
absent in prox. and dist.	0	0
present in prox. and dist.	9	9.5
Edema		
absent in prox. and dist.	0	0
present in prox. and dist.	4.5	7.5
Crêpe-paper	-	-
absent in prox. and dist.		
present in prox. and dist.		
Sum of the score	100	100

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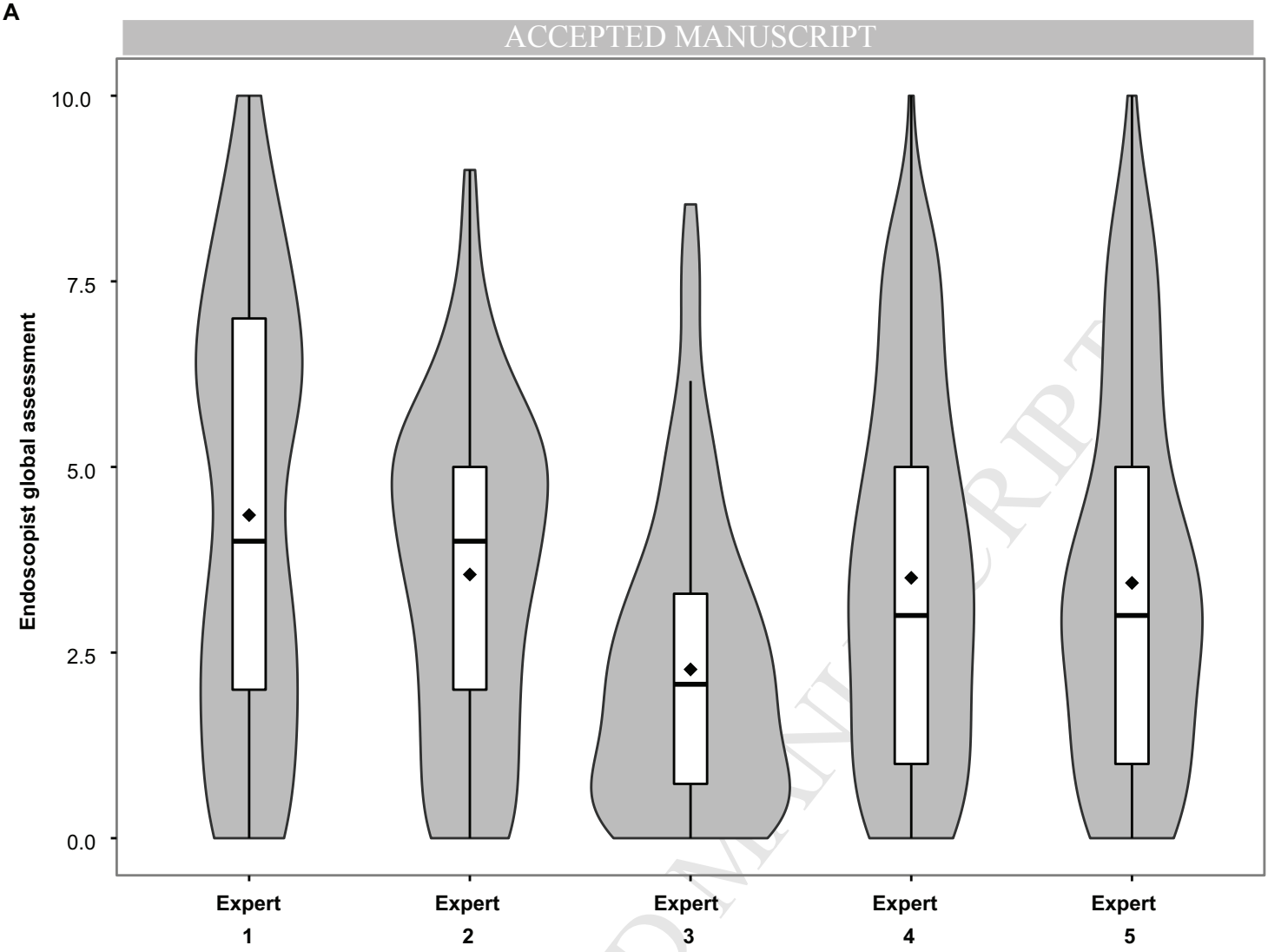
A



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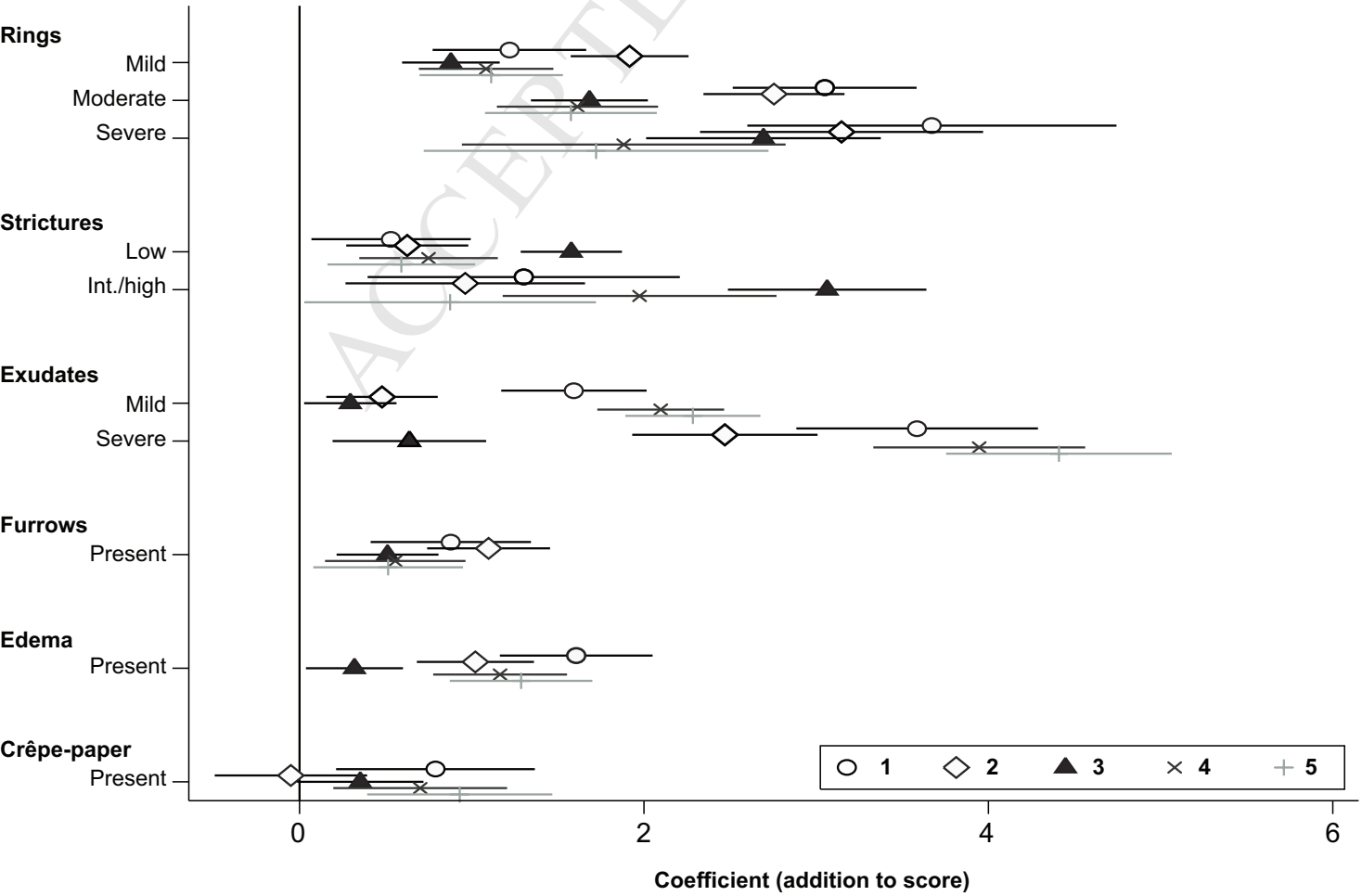
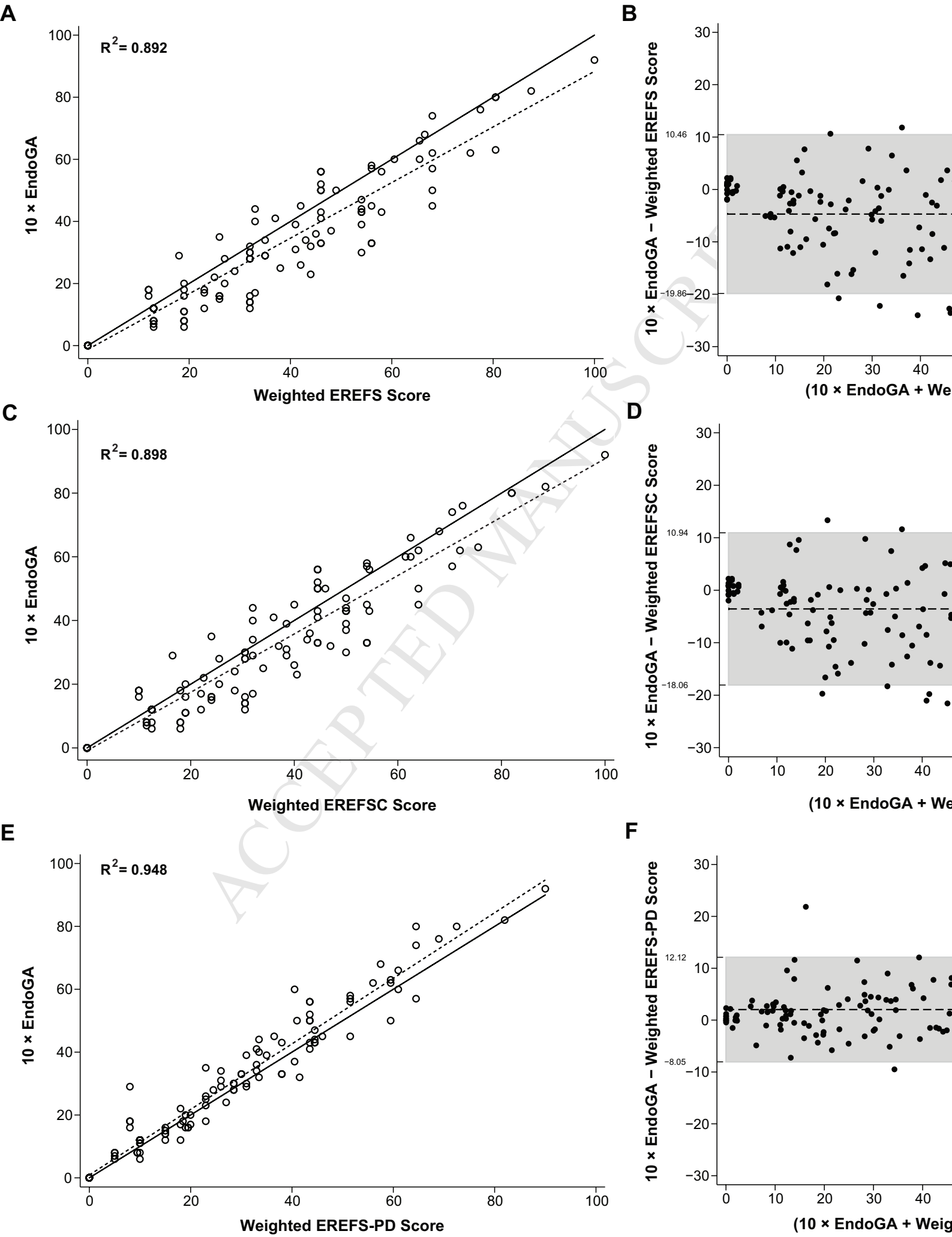




WHAT YOU NEED TO KNOW

BACKGROUND

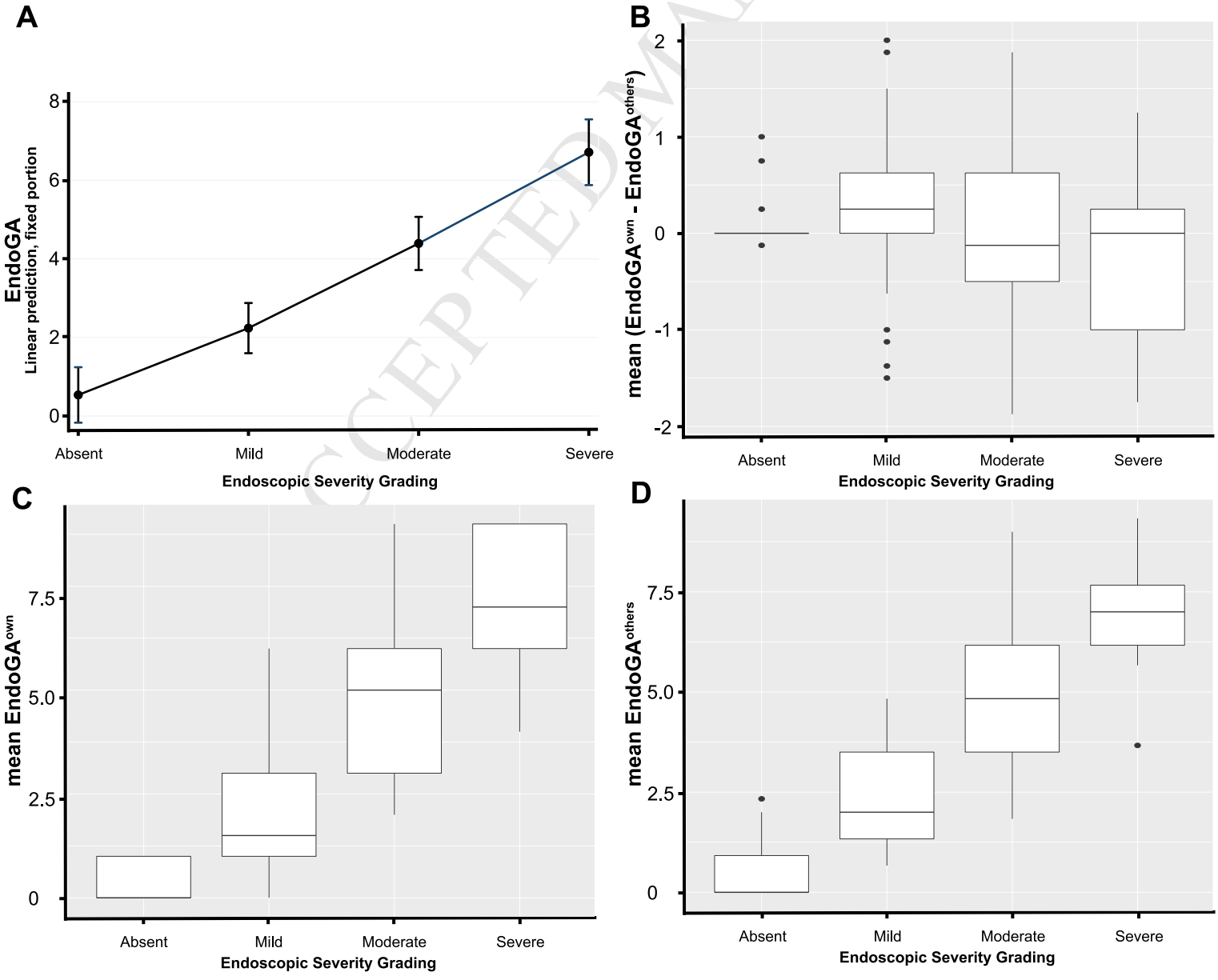
In eosinophilic esophagitis, endoscopic activity is graded by examining the presence and severity of Edema, Rings, Exudates, Furrows, and Strictures (EREFS). As there is paucity of data, we examined variation in the way experts assessed endoscopic severity, developed and validated three EREFS-based scores, and evaluated the scores' responsiveness in clinical trial of fluticasone.

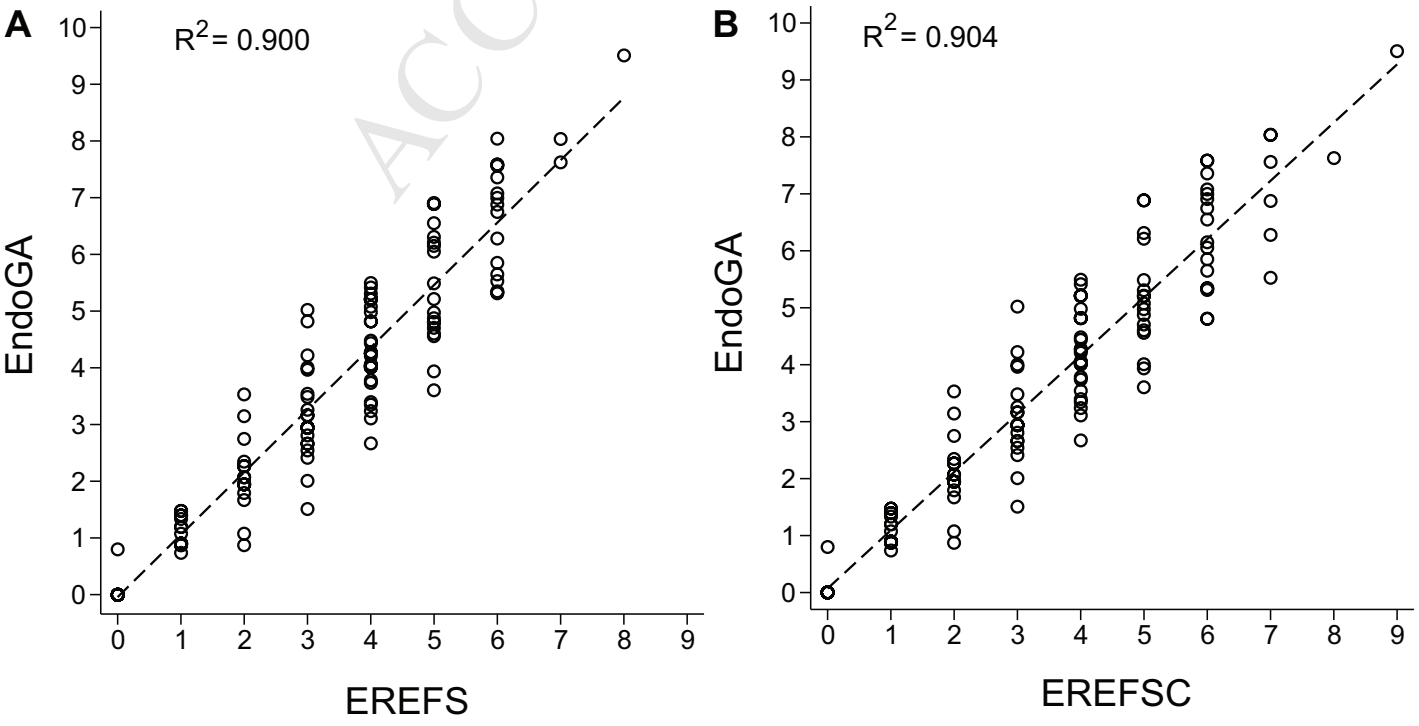
NEW FINDINGS

The endoscopic severity impression differs among expert endoscopists. Exudates accounted for most variation in severity assessment. The responsiveness of new scores considering expert opinion was no better than that of simple score (features given arbitrary values from 0-3), when clinical trial data were analyzed.

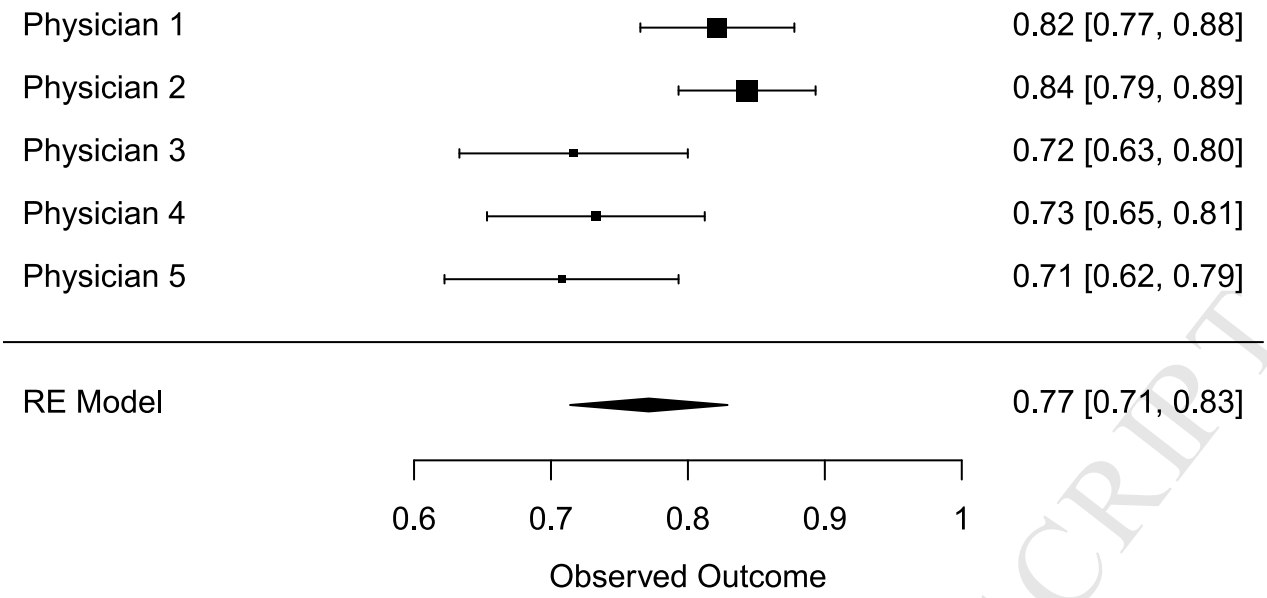
IMPLICATIONS FOR PATIENT CARE

The simple EREFS score should be used in short-term clinical trials of anti-inflammatory therapies. The new score should be examined in long-term, observational studies of patients with broader endoscopic severity spectrum.

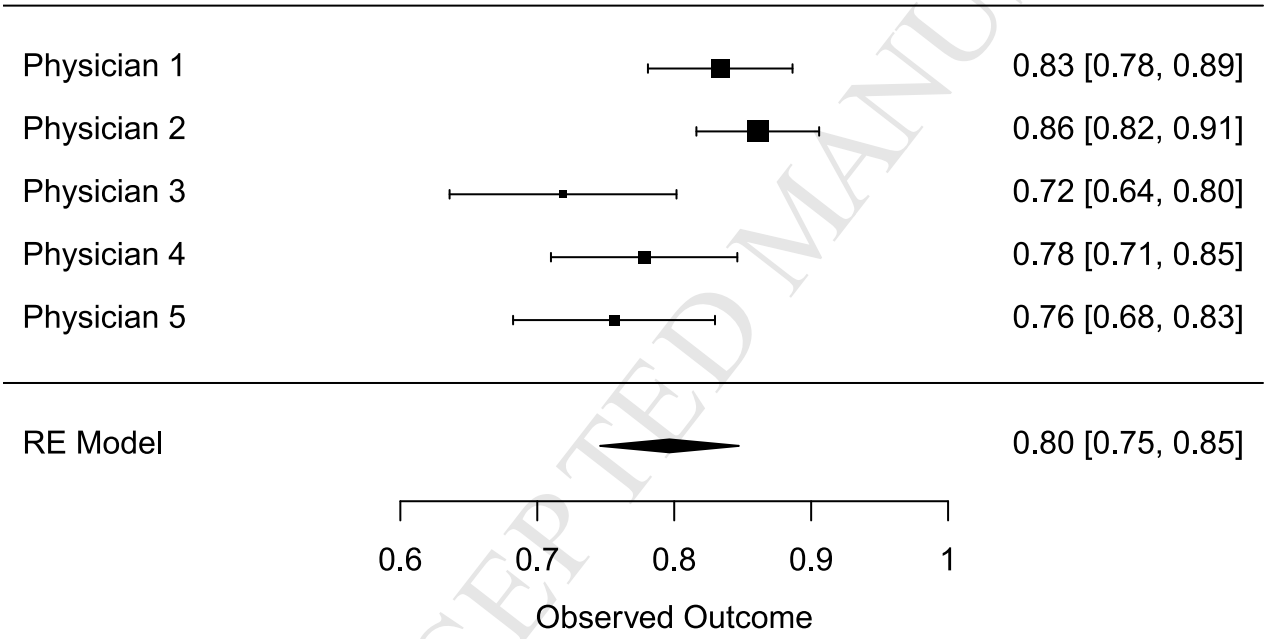




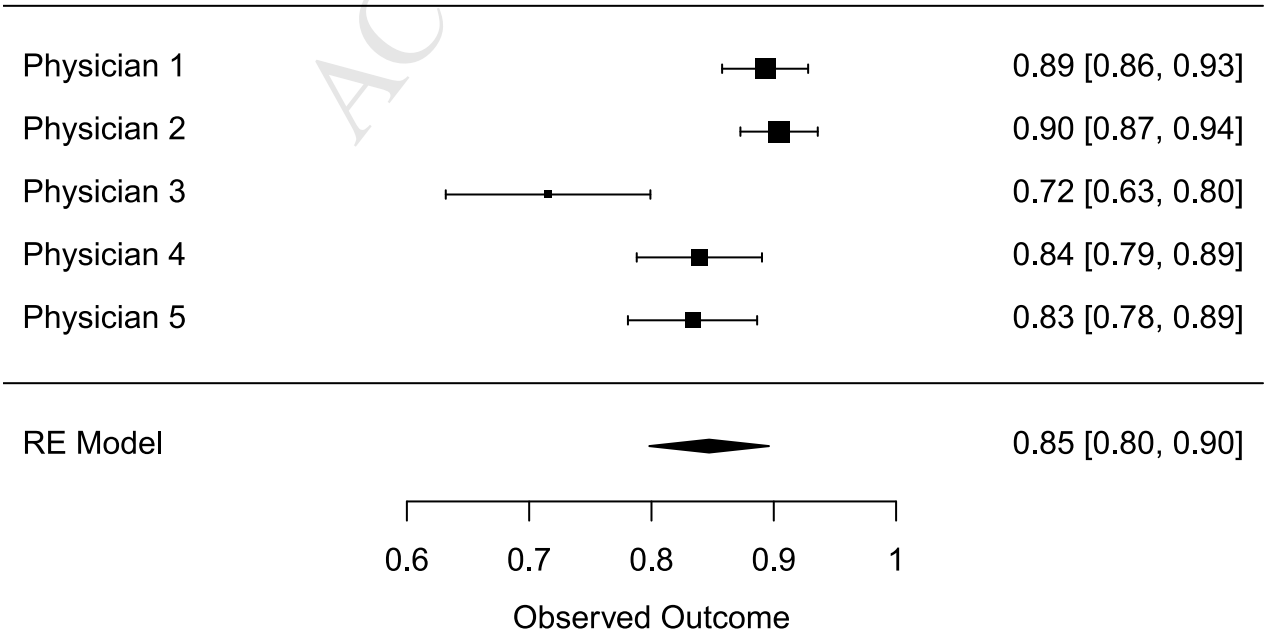
A: R^2 for simple EREFS score

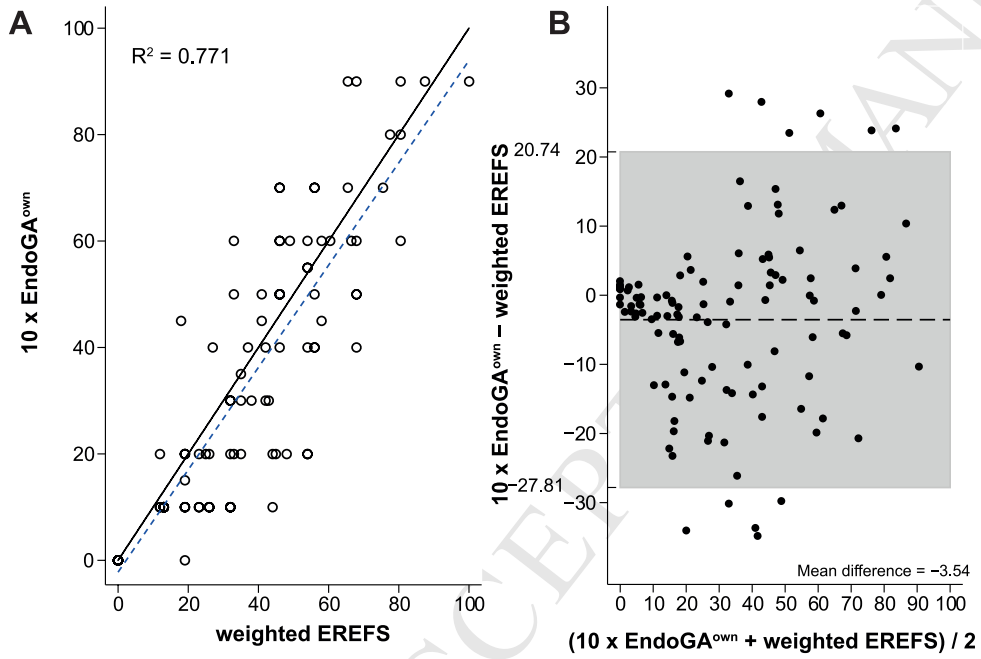


B: R^2 for weighted EREFS score

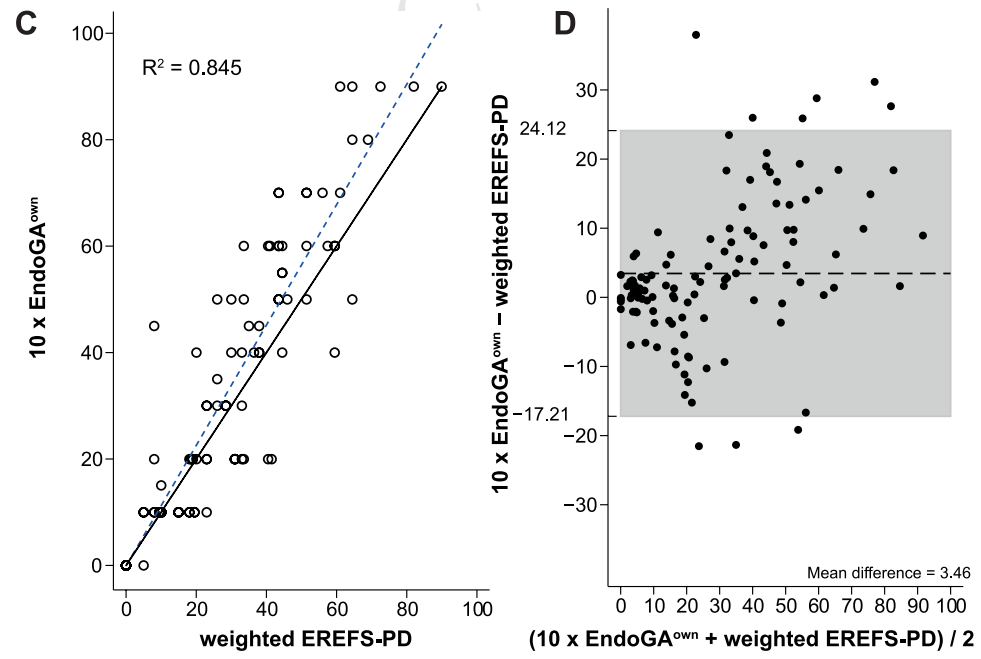


C: R^2 for weighted EREFS-proximal/distal score




A
R² = 0.771
10 x EndoGA^own
weighted EREFS
0
20
40
60
80
100

B
10 x EndoGA^own – weighted EREFS
20.74
−27.81
Mean difference = −3.54
(10 x EndoGA^own + weighted EREFS) / 2
30
20
10
0
−10
−20
−30
0 10 20 30 40 50 60 70 80 90 100


C
R² = 0.845
10 x EndoGA^own
weighted EREFS-PD
0
20
40
60
80
100

D
10 x EndoGA^own – weighted EREFS-PD
24.12
−17.21
Mean difference = 3.46
(10 x EndoGA^own + weighted EREFS-PD) / 2
30
20
10
0
−10
−20
−30
0 10 20 30 40 50 60 70 80 90 100